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## Report

# Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne Syndrome Maps to Chromosome 15q

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**Pyoderma gangrenosum, cystic acne, and aseptic arthritis are clinically distinct disorders within the broad class of inflammatory diseases. Although this triad of symptoms is rarely observed in a single patient, a three-generation kindred with autosomal-dominant transmission of these three disorders has been reported as "PAPA syndrome" (MIM 604416). We report mapping of a disease locus for familial pyoderma gangrenosum–acne–arthritis to the long arm of chromosome 15 (maximum two-point LOD score, 5.83; recombination fraction [$\theta$] 0 at locus *D15S206*). Under the assumption of complete penetrance, haplotype analysis of recombination events defined a disease interval of 10 cM, between *D15S1023* and *D15S979*. Successful identification of a single disease locus for this syndrome suggests that these clinically distinct disorders may share a genetic etiology. These data further indicate the role of genes outside the major histocompatibility locus in inflammatory disease.**

Pyoderma gangrenosum, cystic acne, and aseptic arthritis are clinically distinct members of the large class of inflammatory diseases. Like other disorders that comprise this diverse class, including inflammatory bowel disease, psoriasis, uveitis, and hidradenitis suppurativa, these diseases are frequently syndromal; clinical manifestations of one condition can signal predisposition to development of other inflammatory disorders (Holt et al. 1980; Rosner et al. 1993; Bhalla and Sequeira 1994; Shenefelt 1996). The coincidence of pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA syndrome [MIM 604416]) has been reported as an unusual triad that segregated as an autosomal-dominant disorder in one kindred (Lindor et al. 1997).

Pyoderma gangrenosum is a painful, ulcerating skin disease characterized by erythematous papulopustules that evolve, within days, to necrotic ulcers with elevated, overhanging borders; lesions are located most frequently on the lower limbs or at the sites of minor trauma or surgery (Callen and Taylor 1978). In the most-comprehensive study to date (encompassing 85 patients with pyoderma gangrenosum), 78% of patients manifested at least one additional inflammatory disease, most commonly arthritis or inflammatory bowel disease but also monoclonal gammopathy, hidradenitis suppurativa, and acne conglobata (Powell et al. 1985), among others. In a smaller study, the incidence of associated disease in patients with pyoderma gangrenosum was closer to 50% (Prystowsky et al. 1989). Although pyoderma gangrenosum is not widely considered to be a genetic disorder, three kindreds with autosomal-dominant transmission of pyoderma gangrenosum have been reported (Bundino and Zina 1984; Shands et al. 1987; Girardin et al. 1988).

Cystic acne is a common clinical condition, affecting 10%–20% of adolescents and young adults with varying severity. The pathognomic lesion of cystic acne, most often found on the forehead, cheeks, nose, and chin, is the comedone, a small cyst that forms in a hair follicle when the follicular orifice is blocked by sebum or keratin. Although acne vulgaris, the most common form of cystic acne, is rarely accompanied by other inflammatory disorders, a more-severe form, acne conglobata, characterized by multiple cysts with bridging scars, has been associated with inflammatory arthritis, polyarthralgia, and pyoderma gangrenosum (Cros et al. 1981; Knitzer and Needleman 1991; Piazza and Giunta 1991). Cystic acne is rarely considered to be an inherited disease.

A panoply of arthropathies have been observed in con-

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junction with inflammatory disorders. Joint involvement may be polyarticular or pauciarticular, symmetrical or asymmetrical, and axial or peripheral (Piazza and Giunta 1991; Rosner et al. 1993; Bhalla and Sequeira 1994). Joint inflammation can also have a variety of outcomes, ranging from full recovery to substantial loss of function and destruction of the joint space (Mielants et al. 1987*a;* Gladman 1995). Although aseptic arthritis is rarely associated with acne or pyoderma, it has been tied to inflammatory bowl disease (Mielants et al. 1987*b;* Finch 1989; De Vos et al. 1996), uveitis, hidradenitis suppurativa (Bhalla and Sequeira 1994), and psoriasis (De Vos et al. 1996). The etiology of inflammatory arthritis is likely multifactorial, but genetic predisposition, particularly HLA haplotype (Clemens et al. 1985; Morling et al. 1985; Mielants et al. 1987*b;* Mierau et al. 1988; Puttick et al. 1990), may play an important role.

Our aim was to define the genetic etiology for heritable pyogenic sterile arthritis, pyoderma gangrenosum, and acne. We therefore reviewed the clinical status of family 1R members before we initiated genetic linkage analyses. Twenty-three (56%) surviving members of family 1R (fig. 1*A*) exhibited the pleiotropic features of this syndrome: early childhood onset of intermittent sterile pauciarticular, peripheral erosive arthritis; severe cystic acne beginning in adolescence and persisting into adulthood; and pyoderma gangrenosum. PAPA syndrome was recognized in two children who were initially considered to be unaffected in the clinical report of Lindor et al. (1997). Individual III-5 had arthritis develop at age 8 years, and individual III-9 had pyoderma gangrenosum and acne develop at age 12 years. Some affected individuals had additional findings: six (46%) reported that sterile abscesses formed at the site of parental injections, three (23%) had normocytic pancytopenia develop after taking sulfa-containing medications, and two (15%) experienced sporadic episodes of irritable bowel syndrome. Laboratory evaluations of affected individuals were unrevealing: humoral markers of inflammatory diseases, including erythrocyte sedimentation rate, anti-nuclear antibody, rheumatoid factor, and anticardiolipin antibody, were normal or negative. Cultures of skin and joint fluids were sterile. Joint manifestations of disease were responsive to treatment with a high-dose regimen of corticosteroids. In family 1R, there were two examples of father-to-son transmission and no apparent correlation between the severity of the phenotype and the sex of the subject or his or her affected parent.

After informed consent from the study population was obtained in accordance with institutional guidelines, we performed genetic linkage studies. Polymorphic loci located throughout the human genome were amplified from genomic DNA and were analyzed by use of standard protocols (Weber and May 1989; Watkins et al. 1993). For linkage studies, adult individuals with two or more clinical features of PAPA syndrome were classified as affected. Because medical histories of affected adults indicated that onset of cystic acne occurred after puberty, children and young adolescents were classified as affected if they had pyoderma gangrenosum or steroid-responsive erosive arthritis. LOD scores were calculated by use of the LINKAGE computer program (Lathrop et al. 1984), and we assumed a disease penetrance of .95.

Since certain HLA haplotypes are associated with pyoderma and arthritis, polymorphisms within the MHC class I locus on chromosome 6 were initially analyzed and linkage was excluded (data not shown). Thereafter, a systematic genomewide search was conducted by use of highly polymorphic loci. We analyzed 93 loci, excluding ~70% of the genome, before evidence of linkage was detected with locus *D15S652* (LOD score, 2.37; recombination fraction [$\theta$] 0).

To refine the disease locus, analyses of 15 additional polymorphic loci from this region of chromosome 15q were performed (fig. 1*B*; data not shown). Maximal two-point LOD scores of 5.83 ($\theta = 0$) were obtained with three fully informative loci: *D15S969, D15S206,* and *D15S152,* indicating odds of 20,000:1 that the disease-causing gene is encoded in this region. Maximum two-point LOD scores of 3.31 ($\theta = 0$) were obtained by use of samples from affected individuals only.

A disease haplotype was constructed from genotypes segregating with disease in family 1R (fig. 1*A*). Recombinant haplotypes in eight individuals were analyzed, to determine the boundaries of the disease locus (fig. 1*B*); crossover events in two unaffected individuals (III-13, age 10 years; and III-7, age 9 years) defined a 10-cM disease locus bounded by loci *D15S1023* and *D15S979*. A larger 36-cM interval bounded by *D15S125* and *D15S966* is defined by crossover events in affected individuals III-2 (age 19 years), III-6 (age 11 years), III-11 (age 17 years), and III-12 (age 16 years).

Our results demonstrate that a pleiotropic inflammatory syndrome characterized by pyoderma gangrenosum, cystic acne, and erosive arthritis maps to chromosome 15q between loci *D15S1023* and *D15S979*. Although identification of a single disease locus provides indirect evidence that these clinically distinct entities share a common genetic component, proof of this hypothesis awaits studies that use cloning and the functional characterization of the causal gene or genes within the identified disease locus.

These data contribute to the growing body of literature that show that mutated genes outside the MHC locus can cause inflammatory disease. Genetic studies of inflammatory disorders once focused on the identification of predisposing HLA haplotypes, most significantly HLA-B27, in populations of patients with ankylosing spondylitis, sacroiliitis, psoriasis, and pyoderma (Wood-

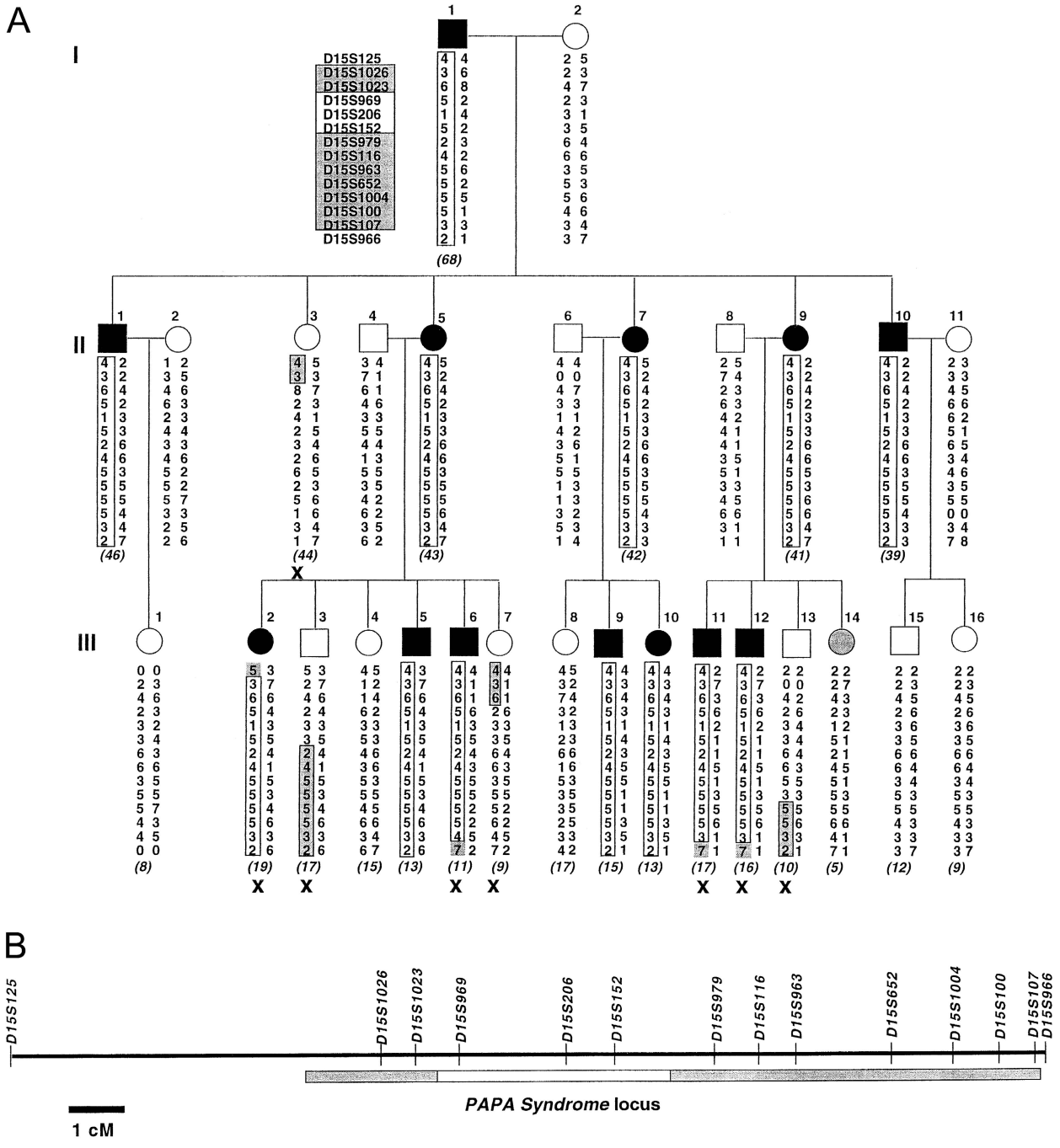


**Figure 1** *A*, Pedigree of family 1R and PAPA-syndrome disease haplotypes. The clinical status (*blackened symbols*, affected; *unblackened symbols*, unaffected; *gray-shaded symbols*, unknown status) and age (*italicized in parentheses*) of individuals are indicated. Alleles of loci on chromosome 15 (centromere to telomere) are provided, and the disease haplotype is boxed. Alleles that are discordant with clinical status are shaded. *B*, Schematic map of chromosome 15q loci studied in family 1R, based on sex-averaged genetic distances from the Genetics Location Database. Discordant haplotypes (indicated by "X" on the pedigree) in unaffected individuals defined a 10-cM disease locus bounded by loci *D15S1023* and *D15S979* (*unblackened bar*). Discordant haplotypes in affected individuals define a 36-cM interval (*gray-shaded bar*) bounded by *D15S125* and *D15S966*.

row 1985; Archer et al. 1988; Mierau et al. 1988). Although these studies were successful in cataloging causative MHC allotypes, how these alleles predispose their carriers to inflammatory disease remains a thorny, yet fundamental, question.

Recently, several groups have used linkage analysis to identify inflammatory-bowel-disease loci outside the MHC gene cluster. In addition to the locus for PAPA syndrome reported here, loci for inflammatory bowel disease have been mapped on chromosomes 3, 7, 12, and 16 (Naom et al. 1997; Binder and Orholm 1996; Ohmen et al. 1996; Parkes et al. 1996; Satsangi et al. 1996). A systemic granulomatous syndrome characterized by inflammatory arthritis, skin rash, and uveitis has been mapped to chromosome 16 (Tromp et al. 1996). Elucidation of the causative genes at these loci has lagged behind the identification of disease intervals, and, to date, non-MHC inflammatory disease genes remain unknown.

Several intriguing candidate genes have been mapped to the disease locus identified by these linkage studies. The leukocyte chemoattractant factor gene (IL-16) located on chromosome 15q25 (Cruikshank et al. 1991) encodes a 56-kD tetrameric glycoprotein produced by activated T cells that stimulates migration of $CD4^+$ lymphocytes and monocytes to areas of inflammation (Cruikshank et al. 1994). It is postulated that IL-16 is an important mediator of T cell and monocyte recruitment by virtue of its action as a soluble ligand for the CD4 receptor (Center et al. 1995). IL-16A protein is a particularly compelling candidate, because of its pivotal role in inflammatory responses and because a unique serum factor that enhances the migration of neutrophils and monocytes has been isolated from a young patient with pyarthrosis and pyoderma gangrenosum (Jacobs and Goetzl 1975).

The gene encoding cellular retinoic acid–binding protein II (CRABP-2) also maps to chromosome 15q25 (Eller et al. 1992). CRABP-2, the predominant form of retinoic acid–binding protein found in the cytoplasm of human skin keratinocytes, may participate in shuttling retinoic acid from the cytoplasm to nuclear receptors or in titrating intracellular concentrations (Astrom et al. 1991; Elder et al. 1992; Eller et al. 1992; Sanquer et al. 1993). Retinoic acid participates in limb morphogenesis and induction of differentiation in skin cells and lymphocytes. Topical administration provides therapeutic benefit in dermatologic conditions (Gilchrest 1996); toxic reactions to retinoic acid include arthralgia, arthritis, leukocytoclastic vasculitis, and erythema nodosum (Dubourg et al. 1996; Pfahl and Chytil 1996; De Francesco et al. 1997). A protein involved in retinoic acid signaling or homeostasis is therefore an appealing candidate for the inflammatory processes of PAPA syndrome.

Whether or not these or other candidate genes are responsible for the heritable disorder in family 1R, the linkage results reported here should foster identification of a gene that, when mutated, causes immune dysregulation and destructive inflammation. We hope that the identification of additional affected families, refined mapping of the disease locus, and ultimately definition of the disease gene will not only improve our understanding of the rare syndrome in this kindred but also contribute to recognition of the full spectrum of inflammatory disorders and etiologies. Ultimately, the elucidation of a shared pathogenesis among this group of diseases may provide insights into the mechanisms by which normally quiescent tissues become erroneously inflamed.

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## Electronic-Database Information

Accession number and URLs for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for PAPA syndrome [MIM 604416])

Genetics Location Database (LDB), http://cedar.genetics.soton.ac.uk/public_html/ldb.html

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